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NEWS 3	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 4	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 5	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 6	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 7	AUG 27	USPATOLD now available on STN
NEWS 8	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 9	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 10	SEP 13	FORIS renamed to SOFIS
NEWS 11	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 12	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 13	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 14	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 15	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 16	OCT 19	BEILSTEIN updated with new compounds
NEWS 17	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 18	NOV 19	WPIX enhanced with XML display format
NEWS 19	NOV 30	ICSD reloaded with enhancements
NEWS 20	DEC 04	LINPADOCDB now available on STN
NEWS 21	DEC 14	BEILSTEIN pricing structure to change
NEWS 22	DEC 17	USPATOLD added to additional database clusters
NEWS 23	DEC 17	IMSDRUGCONF removed from database clusters and STN
NEWS 24	DEC 17	DGENE now includes more than 10 million sequences
NEWS 25	DEC 17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS 26	DEC 17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
NEWS 27	DEC 17	CA/CAplus enhanced with new custom IPC display formats
NEWS 28	DEC 17	STN Viewer enhanced with full-text patent content from USPATOLD
NEWS 29	JAN 02	STN pricing information for 2008 now available
NEWS 30	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS 31	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS 32	JAN 28	MARPAT searching enhanced
NEWS 33	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS 34	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment

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 NEWS 35  JAN 28  MEDLINE and LMEDLINE reloaded with enhancements

 NEWS EXPRESS  19 SEPTEMBER 2007:  CURRENT WINDOWS VERSION IS V8.2,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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luteinizing(w)hormone(w)releasing(w)hormone(w)antagonist) and (0.25(w)mg or
0.5(w)mg)
L1          35 (LHRH(W) ANTAGONIST OR LUTEINIZING(W) HORMONE(W) RELEASING(W)
               HORMONE(W) ANTAGONIST) AND (0.25(W) MG OR 0.5(W) MG)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           25 DUP REM L1 (10 DUPLICATES REMOVED)

=> dis ibib abs l2 1-25

L2   ANSWER 1 OF 25  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2006:9170  CAPLUS
DOCUMENT NUMBER:          144:143245
TITLE:                    Bifunctional gonadotropin-releasing hormone
                          antagonist-progesterone analogs with increased
                          efficacy and duration of action
AUTHOR(S):                Ratcliffe, Karen E.; Fraser, Hamish M.; Sellar, Robin;
                          Rivier, Jean; Millar, Robert P.
CORPORATE SOURCE:         Medical Research Council Human Reproductive Sciences
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Unit, The Queen's Medical Research Institute, Edinburgh, EH16 4TJ, UK
SOURCE: Endocrinology (2006), 147(1), 571-579
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB GnRH peptide analogs are widely used to treat diverse clin. conditions. However, they have poor oral activity and exhibit rapid metabolic clearance, thus requiring injection and depot formulation. Because steroid hormones are bound to plasma proteins, the authors explored the possibility of conjugating hydroxylated progesterones to GnRH analogs to reduce metabolic clearance of the peptides. Conjugation of [D-Lys6]GnRH agonist to the α11-hydroxyl of α11-hydroxyl progesterone via a hemi-succinate bridge increased the plasma half-life after iv injection in rabbits by 3.6-fold while retaining high binding affinity, thus providing proof of concept. Five GnRH antagonists were then synthesized with 21-hydroxyprogesterone conjugated via C21-hydroxyl to positions six (conjugates A and B) and position seven (conjugates C and D) of GnRH antagonists. In the fifth compound the N-terminus of a GnRH antagonist lacking the first two amino acids was conjugated via the C21-hydroxyl to 21-hydroxyprogesterone (conjugate E). All five analogs bound to guinea pig progesterone binding globulin with relatively high affinities (264-1020 nM). Moreover, all five conjugates retained high progestogenic activity in stimulating a progesterone-response-element-driven chloramphenicol acetyltransferase reporter gene in the T47D breast cancer cell line. Conjugation via the ε-amino function of D-Lys6 (conjugates A and B) produced compds. with high binding affinity for the human GnRH receptor (15 and 7 nM) comparable to that of the unconjugated GnRH antagonists (4 and 26 nM). Conjugation via the ε-amino function of Lys7 (conjugates C and D) or the N-terminus of an N-terminally truncated antagonist (conjugate E) produced compds. of low binding affinity. Conjugates A and B also exhibited high functional antagonism of GnRH stimulation of inositol phosphate production in COS-7 cells expressing the human GnRH receptor (2.6 and 16 nM) compared with the unconjugated antagonists (1.3 and 122 nM). In accordance with their poor receptor binding affinity, conjugates C, D, and E had poor functional antagonism. Preliminary dose-finding studies in female marmosets showed transitory progesterone inhibition by 0.25 mg and prolonged suppression of 12 and 17 d by 0.5- and 1.0-mg doses. Injection of conjugate A in adult male marmosets (0.5 mg s.c.) rapidly suppressed plasma testosterone levels, which remained suppressed for at least 3 d. In contrast, the unconjugated parent antagonist alone or with progesterone suppressed testosterone for only 8 h to 1 d. The findings demonstrate that conjugation of progesterone to GnRH antagonists conveys plasma binding and progestogenic properties and increases their efficacy and duration of action in vivo. These new GnRH antagonists show promise as therapeutic agents for hormone-dependent diseases and as contraceptives.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:182426 CAPLUS
DOCUMENT NUMBER: 142:233845
TITLE: LHRH-antagonists in the treatment of fertility disorders
INVENTOR(S): Bouchard, Philippe; Frydman, Rene; Devroey, Paul; Diedrich, Klaus; Engel, Jurgen
PATENT ASSIGNEE(S): Fr.
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont. of U.S. Ser. No. 786,937.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005049200	A1	20050303	US 2003-661780	20030915
PRIORITY APPLN. INFO.:			US 1996-11282P P	19960207
			US 1997-786937 B2	19970122

AB A method of treating infertility disorders by (1) administering an LH-RH antagonist, preferably Cetrorelix, in amts. to selectively suppress endogenous LH but not FSH secretion and (2) inducing follicle growth by administration of exogenous gonadotropin. The selective suppression OF LH allows FSH secretion to be at natural levels thereby not affecting individual estrogen development. The LH-RH antagonist can be given as a single or dual s.c. dose in the range of 1 mg to 10 mg, preferably 2 mg-6 mg. In multiple dosing-posol., LH-RH antagonist can be administered s.c. in an amount in the range of 0.1 to 0.5 mg of LH-RH antagonist/day. LH-RH antagonist is applied starting cycle day 1 to 10, preferably on day 4 to 8, and ovulation can be induced between day 9 and 20 of the menstruation cycle by administering rec. LH, native LH-RH, LH-RH agonist or by HCG. In addition rec. LH, native LH-RH or LH-RH agonist can be given to avoid hyperstimulation syndrome and native LH-RH or a LH-RH agonist can be administered to avoid luteal phase stimulation by neutralizing the neg. effects of HCG.

L2 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2005:1110537 CAPLUS
DOCUMENT NUMBER: 143:399986
TITLE: Effects of testosterone and levonorgestrel combined with a 5α-reductase inhibitor or gonadotropin-releasing hormone antagonist on spermatogenesis and intratesticular steroid levels in normal men
AUTHOR(S): Matthiesson, Kati L.; Stanton, Peter G.; O'Donnell, Liza; Meachem, Sarah J.; Amory, John K.; Berger, Richard; Bremner, William J.; McLachlan, Robert I.
CORPORATE SOURCE: Prince Henry's Institute of Medical Research and Department of Obstetrics and Gynecology, Monash Medical Center, Monash University, Clayton, Victoria, 3168, Australia
SOURCE: Journal of Clinical Endocrinology and Metabolism (2005), 90(10), 5647-5655
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Context: Combination of a GnRH antagonist (acyline), types I and II, 5α-reductase inhibitor (dutasteride) or levonorgestrel (LNG) with testosterone (T) treatment may augment the suppression of spermatogenesis and intratesticular (iT) steroids. Objective: The objective of this study was to assess the effects of combined hormonal contraceptive regimens on germ cell populations and iT steroids. Design, Setting, and Participants: Twenty-nine normal health men enrolled in this prospective, randomized, 14-wk study at the University of Washington. Intervention(s): Twenty-two men received 8 wk of T enanthate (TE; 100 mg, i.m., weekly) combined with (1) 125 μg LNG daily, orally; (2) 125 μg LNG plus 0. 5 mg dutasteride daily, orally; (3) 300 μg/kg acyline twice weekly, s.c.; or (4) 125 μg LNG daily, orally, plus 300 μg/kg acyline twice weekly, s.c. Subjects then underwent a vasectomy and

testicular biopsy. Control men proceeded directly to surgery. Main Outcome Measure(s): The main outcome measures were germ cells and iT steroids [T, dihydrotestosterone, 3α- and β-androstanediol (Adiol), and estradiol (E2)]. Results: High iT levels of all androgens (6- to 123-fold serum levels) and E2 (407-fold serum levels) were found in control men. The iT T (1.9 - 2.6% control) and iT 3βAdiol (16 - 34% control) levels decreased with all treatments. The iT dihydrotestosterone (13 - 29% control) and iT 3αAdiol (44 - 47% control) levels decreased with all but the TE plus LNG treatment. The iT E2 levels decreased only in the TE plus acyline group (28% control). Germ cells from type B spermatogonia onward were suppressed, with no differences between groups found. Variable sites of impairment of germ cell progression were evident between men (spermagonial maturation, meiosis 1 entry, and spermiation). Other than a neg. correlation between iT 3αAdiol and haploid germ cell number, no correlations between germ cell number and gonadotropins, sperm concentration, or iT steroids were found. Conclusions: A similar high testicular:serum gradient exists for E2 and T in normal men, and 8 wk of gonadotropin suppression markedly reduces iT T, with 5α-reduced androgens and E2 levels decreasing to a much lesser degree. The heterogeneity of the germ cell response, regardless of treatment, gonadotropins or iT steroids, points to the individual sensitivity of sites in germ cell development, which is worthy of addnl. exploration.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:357532 CAPLUS

DOCUMENT NUMBER: 143:91168

TITLE: Recombinant luteinizing hormone supplementation to recombinant follicle-stimulating hormone induced ovarian hyperstimulation in the GnRH-antagonist multiple-dose protocol

AUTHOR(S): Griesinger, G.; Schultze-Mosgau, A.; Dafopoulos, K.; Schroeder, A.; Schroer, A.; von Otte, S.; Hornung, D.; Diedrich, K.; Felberbaum, R.

CORPORATE SOURCE: University Clinic of Schleswig Holstein, Campus Luebeck, Luebeck, 23858, Germany

SOURCE: Human Reproduction (2005), 20(5), 1200-1206
CODEN: HUREEE; ISSN: 0268-1161

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Suppression of endogenous LH production by mid-follicular phase GnRH-antagonist administration in controlled ovarian hyperstimulation protocol using recombinant (rec) FSH prepns. void of LH activity may potentially affect ovarian response and the outcome of IVF treatment. The present study prospectively assessed the effect of using a combination of recFSH and recLH on ovarian stimulation parameters and treatment outcome in a fixed GnRH-antagonist multiple dose protocol. A total of 127 infertile patients with an indication for IVF or ICSI were recruited and randomized (using sealed envelopes) to receive a starting dose of either 150 IU recFSH (follitropin α) or 150 IU recFSH plus 75 IU recLH (lutropin α) for ovarian hyperstimulation. GnRH-antagonist (Cetrorelix) 0.25 mg was administered daily from stimulation day 6 onwards up to and including the day of the administration of recombinant HCG (chorion gonadotropin α). Gonadotropin dose adjustments were allowed from stimulation day 6 onwards, HCG was administered as soon as three follicles ≥18 mm were present. The primary outcome parameter was treatment duration until administration of HCG. Exogenous LH did not shorten the time necessary to reach ovulation induction criteria. Serum estradiol (E2) and LH levels

were significantly higher on the day of HCG administration in the recLH-supplemented group (1924.7 vs. 1488.3 pg/mL, and 2.1 vs. 1.4 IU/l, resp.). Thus, except for higher E2 and LH levels on the day of HCG administration, no pos. trend in favor of addnl. LH was found as defined by treatment outcome parameters.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:59356 CAPLUS

DOCUMENT NUMBER: 142:233478

TITLE: Novel male hormonal contraceptive combinations: The hormonal and spermatogenic effects of testosterone and levonorgestrel combined with a 5α-reductase inhibitor or gonadotropin-releasing hormone antagonist

AUTHOR(S): Matthiesson, Kati L.; Amory, John K.; Berger, Richard; Ugoni, Antony; McLachlan, Robert I.; Bremner, William J.

CORPORATE SOURCE: Prince Henry's Institute of Medical Research and Department of Obstetrics and Gynaecology, Monash Medical Centre, Monash University, Clayton, 3168, Australia

SOURCE: Journal of Clinical Endocrinology and Metabolism (2005), 90(1), 91-97
CODEN: JCEMAZ; ISSN: 0021-972X

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors postulated that the addition of a combined types I and II, 5α-reductase inhibitor (dutasteride) or long-acting GnRH antagonist (acyline) to combination testosterone plus levonorgestrel treatment may be advantageous in the suppression of spermatogenesis for male contraception. This study aimed to examine effects of novel combination contraceptive regimens on serum gonadotropins and androgens and sperm concentration This study was divided into three phases: screening (2 wk), treatment (8 wk), and recovery (4 wk). Twenty-two men (-6/group) received 8 wk of treatment with testosterone enanthate (TE, 100 mg i.m. weekly) combined with one of the following:. 1) Levonorgestrel (LNG) 125 μg orally daily;. 2) LNG 125 μg plus dutasteride 0.5 mg orally daily;. 3) Acyline 300 μg/kg s.c. every 2 wk (as a comparator for any addnl. progestin effects); or. 4) LNG 125 μg orally daily plus acyline 300 μg/kg s.c. every 2 wk. Serum gonadotropin levels were similarly suppressed by all treatments, falling to a nadir between 1.2 and 3.4% and 0.5 and 0.8% baseline for FSH and LH, resp. Serum dihydrotestosterone levels were significantly decreased in the dutasteride group throughout the treatment period to a nadir of 31% baseline (wk 7). No significant differences in sperm concns. among treatment groups were seen. Severe oligospermia (0.1-3 million/mL) or azoospermia was seen in none of five and four of five in TE + LNG; two of six and four of six in TE + LNG + dutasteride; two of six and four of six in TE + acyline; and one of five and three of five in TE + LNG + acyline groups, resp. There was one non-responder in each of the TE + LNG and TE + LNG + acyline groups. The authors conclude that the addition of a combined types I and II, 5α-reductase inhibitor or long-acting GnRH antagonist to a testosterone plus LNG regimen provides no addnl. suppression of gonadotropins or sperm concentration over an 8-wk treatment period. However, further evaluation of the effects of these regimens on the testis (including testicular steroid levels and germ cell maturation) and the treatment of larger nos. of men (and for longer periods) may provide data to support their place in contraceptive development.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:1068574 CAPLUS
DOCUMENT NUMBER: 142:233468
TITLE: Restoration of endocrine and ovarian function after stopping GnRH antagonist treatment in goats
AUTHOR(S): Gonzalez-Bulnes, A.; Lopez-Sebastian, A.; Garcia-Garcia, R. M.; Veiga-Lopez, A.; Souza, C. J. H.; McNeilly, A. S.
CORPORATE SOURCE: Departamento de Reproduccion Animal INIA, Madrid, 28040, Spain
SOURCE: Theriogenology (2005), 63(1), 83-91
CODEN: THGNBO; ISSN: 0093-691X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have tested if the high number of unfertilized ova and degenerated embryos found in superovulated goats previously treated with GnRH antagonist can be related to a prolongation of gonadotrophin down-regulation and/or alterations in follicular function during the period of administration of the superovulatory treatment, around 4 days after the end of the antagonist treatment. A total of 15 does were treated with intravaginal progestagen sponges and daily injections of 0.5 mg of the GnRH antagonist Antarelix for 6 days, while 5 does acted as controls receiving saline. During the antagonist treatment, the mean plasma LH concentration was lower in treated than control goats (0.5 vs. 7 ng/mL); however, the FSH levels remained unaffected (0.8 vs. 8 ng/mL). In this period, treated does also showed an increase in the number of small follicles with 2-3 mm in size (10.7 vs. 8.4), and a decrease in both the number of follicles ≥4 mm in size (5.0 vs. 6.8) and the secretion of inhibin A (120.9 vs. 151.6 pg/mL). After cessation of the antagonist treatment, there was an increase in LH levels in treated goats from the day after the last Antarelix injection (Day 1), so that LH levels were the same as controls on Day 3 (0.6 vs. 0.6 ng/mL). However, there were even greater nos. of small follicles than during the period of antagonist injections (15.4 in treated vs. 8.9 in control). Moreover, the number of ≥4 mm follicles and the secretion of inhibin A remained lower in treated goats (3.9 follicles and 84.4 pg/mL vs. 5.4 follicles, and 128.9 pg/mL). These results indicate that pituitary secretion of gonadotrophins is restored shortly after the end of antagonist treatment, but activity of ovarian follicles is affected.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 7 OF 25 BIOSIS COPYRIGHT (c) 2008 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:470830 BIOSIS
DOCUMENT NUMBER: PREV200400466840
TITLE: Development and validation of a HPLC method for routine quantification of the decapeptide Cetrorelix in liposome dispersions.
AUTHOR(S): Grohganz, Holger [Reprint Author]; Schlafli, Oliver; Rischer, Matthias; Brandl, Martin
CORPORATE SOURCE: Inst PharmDept Pharmaceut and Biopharmaceut, Univ Tromso, N-9037, Tromso, Norway
holgerg@farmasi.uit.no
SOURCE: Journal of Pharmaceutical and Biomedical Analysis, (March 10 2004) Vol. 34, No. 5, pp. 963-969. print.
CODEN: JPBADA. ISSN: 0731-7085.
DOCUMENT TYPE: Article
LANGUAGE: English

ENTRY DATE: Entered STN: 9 Dec 2004
Last Updated on STN: 9 Dec 2004

AB The development and validation of an HPLC method for the quantification of the decapeptide Cetrorefix (acetyl-D-2-naphthylalanyl-D-4-chlorphenylalanyl-D-3-pyridylalanyl-seryl-tyrosyl-D-citrullyl-leucyl-arginyl-prolyl-D-alaninamide), a potent antagonist of the luteinising hormone-releasing hormone in liposome dispersions is described. An isocratic reversed phase method with UV-detection appeared most appropriate. Several detergents were tried to disrupt liposomes. Furthermore, detergents turned out to be useful, because they minimised unwanted loss of Cetrorelix due to adsorption to the vial surfaces. Triton X-100 was found most effective, while sodium cholate led to quantification problems. In the presence of 2.5% Triton X-100 calibration curves with a high degree of linearity were achieved in the desired range of 0.2-10 mug/ml. The limits of detection and quantification of Cetrorelix were calculated from the peak-to-noise ratio to be 11 and 37 ng/ml, respectively. The repeatability of the method in presence of phospholipid and Triton was good with relative standard deviations (R.S.D.) ranging from 0.8% (at 0.05 mug/ml) to 1.5% (at 0.2 mug/ml). The presence of liposomes at phospholipid contents of up to 0. 25 mg/ml did not significantly affect the slope or linearity of the calibration curve, nor the peak-to-noise ratio.

L2 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:518356 CAPLUS
DOCUMENT NUMBER: 139:333259
TITLE: The administration of the GnRH antagonist, cetrorelix, to oocyte donors simplifies oocyte donation
AUTHOR(S): Thong, K. J.; Yong, P. Y.; Menezes, Q.
CORPORATE SOURCE: Assisted Conception Programme, Edinburgh Fertility and Reproductive Endocrine Centre, Edinburgh, EH16 4SA, UK
SOURCE: Human Reproduction (2003), 18(6), 1256-1258
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors report their experience on the efficacy of a new regimen of the GnRH antagonist, cetrorelix, and recombinant FSH, Gonal-F, for controlled ovarian stimulation in a donor oocyte program. Six oocyte donors were commenced on Gonal-F (150 IU) and two on Gonal-F 225 IU daily on day 4 together with cetrorelix 0.25 mg daily on day 8 until the day of administration of hCG. Six premenopausal recipients were down-regulated with intranasal Nafarelin 400 μg twice daily; two women with premature menopause did not require down-regulation for synchronization between donor and recipient cycles. The median (range) of oocytes retrieved and the median (range) fertilization rates were 7 (3-13) and 50% (0-71%) resp. With the exception of a recipient who had failed fertilization, seven recipients had two embryos transferred. The median (range) number of days of ovarian stimulation, cetrorelix administration and number of Gonal-F ampoules administered for ovarian stimulation were 9 (7-12) days, 5 (3-8) and 18 (14-24) resp. The clin. pregnancy rate per cycle was 50% (4/8) and one of the latter women miscarried at eight weeks gestation. Three women (37.3%) had full term deliveries. This preliminary study has shown that using a combination of cetrorelix and Gonal-F resulted in a high pregnancy rate, reduced the duration of treatment for the donor and simplified oocyte donation.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 25 MEDLINE on STN
ACCESSION NUMBER: 2002709676 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12470526
TITLE: Rescue IVF and coasting with the use of a GnRH antagonist after ovulation induction.
AUTHOR: Fatemi Human Mousavi; Platteau Peter; Albano Carola; Van Steirteghem Andre; Devroey Paul
CORPORATE SOURCE: Centre for Reproductive Medicine, Dutch-Speaking Free University of Brussels, Laarbeeklaan 101, 1090 Brussels, Belgium.. hmousavi@az.vub.ac.be
SOURCE: Reproductive biomedicine online, (2002 Nov-Dec) Vol. 5, No. 3, pp. 273-5.
Journal code: 101122473. ISSN: 1472-6483.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 17 Dec 2002
Last Updated on STN: 31 Jan 2003
Entered Medline: 30 Jan 2003

AB The major risks of exogenous gonadotrophin therapy for ovulation induction in a patient with polycystic ovaries (PCO) are multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). This case report describes a 23-year-old patient, who was referred to the Centre for Reproductive Medicine in Brussels because of a high risk of developing OHSS and rising LH following ovulation induction with a low-dose step-up protocol using gonadotrophins. After counselling the patient, the decision was made to perform a rescue IVF cycle. The patient was first coasted with 0 .25 mg ganirelix; the serum oestradiol concentrations decreased and the LH peak was successfully suppressed. No OHSS occurred. An ongoing twin pregnancy was achieved after the transfer of two embryos. This case report demonstrates the feasibility of coasting with LH-releasing hormone (LHRH) antagonists (0. 25 mg ganirelix) and the usefulness of the antagonists for ovulation induction cycles in patients who need rescue IVF.

L2 ANSWER 10 OF 25 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2002259522 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11998957
TITLE: Plasma and follicular fluid concentrations of LHRH antagonist cetrorelix (Cetrotide) in controlled ovarian stimulation for IVF.
AUTHOR: Ludwig M; Albano C; Olivennes F; Felberbaum R E; Smitz J; Ortmann O; Romeis P; Niebch G; Pechstein B; Riethmuller-Winzen H; Devroey P; Diedrich K
CORPORATE SOURCE: Department of Gynecology and Obstetrics, Medical University of Lubeck, Germany.. Ludwig_M@t-online.de
SOURCE: Archives of gynecology and obstetrics, (2002 Jan) Vol. 266, No. 1, pp. 12-7.
Journal code: 8710213. ISSN: 0932-0067.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 10 May 2002
Last Updated on STN: 8 Oct 2002
Entered Medline: 4 Oct 2002

AB Cetrorelix was administered in differing daily dosages for controlled ovarian stimulation. The dosage levels were 3 mg (9 cycles), 1 mg (19 cycles), 0.5 mg (43 cycles), 0. 25 mg (46 cycles) and 0.1 mg (7 cycles). In the 3 mg, 1

mg and 0.5 mg group the respective median plasma concentrations of cetrorelix on the day of oocyte pick-up (OPU) were 2.10 ng/ml, 1.42 ng/ml and 0.88 ng/ml and 1.03 ng/ml, 0.46 ng/ml and 0.49 ng/ml on the day of embryo transfer (ET). In the 0. 25 mg and 0.1 mg groups plasma cetrorelix levels were below the limit of quantification. The cetrorelix concentrations in follicular fluid (FF) in the 0.25 mg group were detectable in only 14 out of 44 samples, while in the 0.1 mg group no detectable concentrations could be obtained. We also examined 80 cycles after single doses of 5 mg (7 cycles), 3 mg (42 cycles), and 2 mg (31 cycles) cetrorelix. On the day of OPU the respective median plasma concentrations of cetrorelix were 0.57 ng/ml, 0.62 ng/ml, and 0.56 ng/ml, and 0.61 ng/ml and 0.28 ng/ml on the day of ET in the 5 mg and 3 mg groups. In the 2 mg group, the plasma concentrations fell to below limits of quantification in 8/9 samples on the day of ET. In 26 out of 27 FF samples cetrorelix was detectable in the 3 mg single dose group (median level: 0.69 ng/ml).

L2 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:886135 CAPLUS
DOCUMENT NUMBER: 136:96372
TITLE: Comparison of luteal phase profile in gonadotrophin stimulated cycles with or without a gonadotrophin-releasing hormone antagonist
AUTHOR(S): Ragni, Guido; Vegetti, Walter; Baroni, Elena; Colombo, Michela; Arnoldi, Mariangela; Lombroso, Giancarlo; Crosignani, Pier Giorgio
CORPORATE SOURCE: Infertility Unit, Department of Obstetrics and Gynaecology, University of Milan, Milan, 20122, Italy
SOURCE: Human Reproduction (2001), 16(11), 2258-2262
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of our study was to explore luteal phase hormone profiles in gonadotropin-stimulated cycles with or without gonadotropin-releasing hormone (GnRH) antagonist therapy during intrauterine insemination (IUI). Forty-one infertile couples were recruited in this randomized clin. study. The 19 patients included in group A were treated for 21 cycles with recombinant FSH 150 IU/day starting from day 3 of the cycle and with the GnRH antagonist cetrorelix at the dose of 0.25 mg/day starting from the day in which a follicle with a mean diameter of ≥14 mm was seen at ultrasound scan. Cetrorelix was administered until human chorionic gonadotropin (HCG) administration. The 22 patients included in group B were administered recombinant FSH alone at the same dosage for 27 cycles. The two treatment groups showed a similar increase in progesterone concentration during the luteal phase. In the mid-luteal phase (day 6 after HCG), estradiol concns. in group B were significantly higher compared with group A but the estradiol:progesterone ratio was similar in the two groups. Serum LH was completely suppressed during the follicular phase only in group A, concomitantly with GnRH antagonist administration. A total of six pregnancies, all ongoing, were achieved (14.3% per patient and 12.2% per cycle), equally distributed in group A and in group B. GnRH antagonists can be safely administered in gonadotropin-stimulated IUI cycles without luteal phase supplementation because no deleterious effects of GnRH antagonist administration were noted on luteal progesterone concentration or on the duration of the luteal phase.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 25 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2000329049 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10872648
TITLE: Pituitary and gonadal endocrine effects and pharmacokinetics of the novel luteinizing hormone-releasing hormone antagonist teverelix in healthy men--a first-dose-in-humans study.
AUTHOR: Erb K; Pechstein B; Schueler A; Engel J; Hermann R
CORPORATE SOURCE: Department of Human Pharmacology, Corporate Research, ASTA Medica AG, Frankfurt am Main, Germany.. KatharinaErb@t-online.de
SOURCE: Clinical pharmacology and therapeutics, (2000 Jun) Vol. 67, No. 6, pp. 660-9.
Journal code: 0372741. ISSN: 0009-9236.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 14 Jul 2000
Last Updated on STN: 14 Jul 2000
Entered Medline: 6 Jul 2000

AB BACKGROUND. Teverelix is a novel synthetic peptidic luteinizing hormone-releasing hormone (LHRH) antagonist. METHODS: Single subcutaneous morning doses of teverelix acetate (either 0.5, 1, 2, 3, or 5 mg base) were investigated in a randomized, single-blind, placebo-controlled, dose-escalating parallel-group design in healthy men. Six subjects received teverelix, and two subjects received placebo per dose level. Blood samples for lutropin, luteinizing hormone (LH), and follitropin, follicle-stimulating hormone (FSH), and testosterone, as well as for pharmacokinetics, were withdrawn up to 120 hours after dosing. Serum hormone levels were determined by electrochemicoluminescence immunoassays, and plasma teverelix concentrations were determined by radioimmunoassay. RESULTS: Teverelix led to a rapid, marked suppression of LH, testosterone and, to a lesser extent, FSH. Median maximum suppressions compared with predose levels were -93% for LH and -54% for FSH after teverelix 5 mg, and -93% for testosterone after teverelix 3 mg, respectively. After 5 mg teverelix, testosterone suppression <1 ng/mL started a median of 12 hours after dosing and lasted for a median of 33 hours. The duration of testosterone suppression increased with dose. Geometric means of peak teverilix plasma concentrations were 4.5 ng/mL (0.5 mg teverelix) to 49.0 ng/mL (5 mg teverelix) and tmax occurred between 1 and 4 hours after dosing. Geometric means of the area under the teverelix plasma concentration-time course from zero to time of the last quantifiable plasma concentration [AUC(O-tlast)] were 54.9 ng x h/mL (0.5 mg teverelix) to 881.8 ng x h/mL (5 mg teverelix). Median values for apparent terminal half-lives ranged from 24 to 75 hours. The most frequently reported adverse events were short-lasting mild injection-site reactions. CONCLUSIONS: Teverelix showed pronounced LH and testosterone suppressive effects after single subcutaneous doses in healthy men. Duration of hormone suppression increased with dose. Teverelix was well tolerated. This profile indicates potential for further clinical use.

L2 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:459854 CAPLUS
DOCUMENT NUMBER: 133:305174
TITLE: Cetrorelix, ASTA Medica AG
AUTHOR(S): Norman, Peter

CORPORATE SOURCE: Norman Consulting, Burnham, Bucks, SL1 8JW, UK
SOURCE: Current Opinion in Oncologic, Endocrine & Metabolic Investigational Drugs (2000), 2(2), 227-248
CODEN: COODF2; ISSN: 1464-8466
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 221 refs. ASTA Medica has developed cetrorelix, an injectable LHRH antagonist for the treatment of sex hormone-dependent disorders such as breast, ovarian and prostate cancers, benign prostate hyperplasia and gynecol. disorders including uterine myoma and endometriosis. Cetrorelix has been launched for the treatment of infertility in Germany, Sweden, Netherlands, Austria and Belgium. The compound is in phase II trials for prostate cancer, benign prostatic hyperplasia and uterus myomatosus. In May 1999, cetrorelix was launched for the treatment of infertility in Germany and the UK, with subsequent launches in Sweden, The Netherlands, Austria and Belgium. In Nov. 1998, the company reported that cetrorelix was undergoing registration for the controlled induction of ovulation and on 13 Apr. 1999, it was approved by the European Commission for marketing in the 15 countries of the EU for the treatment of infertility. ASTA Medica and Ares-Serono intended to file a US NDA submission for cetrorelix in fertility treatment by the end of 1999. Two cetrorelix dosage regimens have been confirmed by EU regulators to avoid LH surge, (i) 0.25 mg powder and solvent solution for injection starting on days 5-6 of follicular stimulation; or (ii), 3 mg cetrorelix as a single dose given on the seventh day of follicular stimulation. The compound is in phase II trials for prostate cancer, benign prostatic hyperplasia and uterus myomatosus. In all three conditions initial reports indicate that 1-2-mo treatment with cetrorelix provides rapid, symptomatic relief. ASTA Medica has formed a joint venture company, Kayaku ASTA Medica Co Ltd, with Nippon Kayaku for joint development of cetrorelix. Cetrorelix is licensed to Shionogi in Japan, where it is in phase II trials. ASTA holds a patent, WO-09500168, for the use of cetrorelix in the treatment of AIDS and AIDS-related disease.

REFERENCE COUNT: 221 THERE ARE 221 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:740190 CAPLUS
DOCUMENT NUMBER: 132:102992
TITLE: Ovarian stimulation for in-vitro fertilization/intracytoplasmic sperm injection with gonadotrophins and gonadotrophin-releasing hormone analogues: agonists and antagonists
AUTHOR(S): Felberbaum, R.; Diedrich, K.
CORPORATE SOURCE: Department of Obstetrics and Gynecology, The Medical University of Lubeck, Lubeck, 23538, Germany
SOURCE: Human Reproduction (1999), 14(Suppl. 1), 207-221
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The gonadotropin-releasing hormone (GnRH) antagonists Cetrorelix and Ganirelix have been used in recent years in clin. studies to prove that these compds. reliably prevent the onset of premature LH surges during ovarian stimulation. Cetrorelix has been applied in single and multiple dose protocols, while Ganirelix has until now only been used in the multiple dose protocol. In the latter protocol, ovarian stimulation is started on day 2 or 3 of the spontaneous cycle with human menopausal gonadotropin or recombinant FSH. Daily administration of the GnRH

antagonist at its min. ED (0.25 mg/day s.c.)
occurs from the sixth day of stimulation onwards until ovulation induction by human chorionic gonadotropin. In the single dose protocol, 3 mg of the GnRH antagonist Cetrorelix was injected on day 8 of the stimulation cycle. Both protocols have been proven to be safe and effective. Fertilization rates of >60% in in-vitro fertilization and >70% in intracytoplasmic sperm injection, as well as clin. pregnancy rates of .apprx.30% per transfer, sound most promising. The incidence of a premature LH surge is below 2%. The incidence of severe ovarian hyperstimulation syndrome seems to be lower under antagonist treatment than in the long agonistic protocol. Treatment time is significantly shortened.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:293389 CAPLUS
DOCUMENT NUMBER: 129:1027
TITLE: Use of LH-RH antagonists as diagnostic agents
INVENTOR(S): Engel, Juergen; Diedrich, Klaus; Felberbaum, Ricardo
PATENT ASSIGNEE(S): Asta Medica A.-G., Germany
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9818482	A1	19980507	WO 1997-DE2456	19971023
W: AU, BR, HU, IL, JP, MX, NO, NZ, PL, RU, SG				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19644994	A1	19980507	DE 1996-19644994	19961030
AU 9852217	A	19980522	AU 1998-52217	19971023
AU 717538	B2	20000330		
EP 938330	A1	19990901	EP 1997-947017	19971023
EP 938330	B1	20020206		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9712456	A	19991019	BR 1997-12456	19971023
NZ 335065	A	20000623	NZ 1997-335065	19971023
HU 9904642	A2	20000628	HU 1999-4642	19971023
JP 2001502702	T	20010227	JP 1998-519885	19971023
AT 212856	T	20020215	AT 1997-947017	19971023
PT 938330	T	20020731	PT 1997-947017	19971023
ES 2172818	T3	20021001	ES 1997-947017	19971023
RU 2193414	C2	20021127	RU 1999-111774	19971023
PL 188998	B1	20050531	PL 1997-333174	19971023
IL 129293	A	20051218	IL 1997-129293	19971023
TW 534817	B	20030601	TW 1997-86115895	19971027
CA 2219641	A1	19980430	CA 1997-2219641	19971028
ZA 9709693	A	19980507	ZA 1997-9693	19971029
US 6106805	A	20000822	US 1997-961085	19971030
NO 9901920	A	19990422	NO 1999-1920	19990422
NO 323690	B1	20070625		

PRIORITY APPLN. INFO.: DE 1996-19644994 A 19961030
WO 1997-DE2456 W 19971023

AB A diagnostic agent for improving the effectiveness of hysteroscopy contains an LH-RH antagonist, especially Cetrorelix, to cause rapid regression of the thickness of the endometrium and thereby improve hysteroscopic visualization of pathol. conditions. The agent is administration before hysteroscopy and/or in preparation for operations, either in a single dose of

0.1-2 mg/kg or in multiple doses of 0.01-0.5 mg/kg by injection, preferably split over 1-14 days. The agent is further suitable for use in hysteroscopy with immediately following noninvasive therapy or surgery of pathol. conditions of the uterus such as myoma and endometrial hyperplasia.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:538778 CAPLUS
DOCUMENT NUMBER: 131:139954
TITLE: LHRH antagonists in the treatment of fertility disorders
INVENTOR(S): Bouchard, Philippe; Frydman, Rene; Diedrich, Klaus; Engel, Jurgen; Devroey, Paul
PATENT ASSIGNEE(S): Asta Medica AG, Germany
SOURCE: Can. Pat. Appl., 15 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

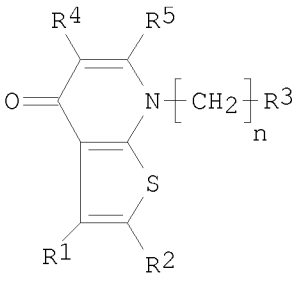
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2200541	A1	19980722	CA 1997-2200541	19970320
PRIORITY APPLN. INFO.:			US 1997-786937 A	19970122

AB A method of treating infertility disorders by administering an LH-RH antagonist, preferably Cetrorelix, in amts. to selectively suppress endogenous LH but not FSH secretion and inducing follicle growth by administration of exogenous gonadotropin. The selective suppression of LH allows FSH secretion to be at natural levels thereby not affecting individual estrogen development. The LH-RH antagonist can be given as a single or dual s.c. dose in the range of 1 mg to 10 mg, preferably 2 mg - 6 mg. In multiple dosing posol., LH-RH antagonist can be administered s.c. in an amount in the range of 0.1 to 0.5 mg of LH-RH antagonist/day. LH-RH antagonist is applied starting cycle day 1 to 10, preferably on day 4 to 8, and ovulation can be induced between day 9 and 20 of the menstruation cycle by administering rec. LH, native LH-RH, LH-RH agonist or by HCG. In addition rec. LH, native LH-RH or LH-RH agonist can be given to avoid hyperstimulation syndrome and native LH-RH or a LH-RH agonist can be administered to avoid luteal phase stimulation by neutralizing the neg. effects of HCG.

L2 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:542142 CAPLUS
DOCUMENT NUMBER: 127:253169
TITLE: LH-RH antagonist compositions
INVENTOR(S): Ishiguro, Toshihiro; Furuya, Shuichi; Suzuki, Nobuhiro
PATENT ASSIGNEE(S): Takeda Seiyaku K. K., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 26 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09208496	A	19970812	JP 1996-14322	19960130
PRIORITY APPLN. INFO.:			JP 1996-14322	19960130
OTHER SOURCE(S):	MARPAT 127:253169			

GI



I

AB LH-RH antagonist compns. contain: (A) thienopyridine compds. e.g. (I) [R1-2 = H or linkage via N, C or S, R3 = (un)substituted polycyclic or other group, R4 = H, formyl, (un)substituted carbony group, etc., R5 = H, or linkage via C, n = 0-3] (prepns. given) as LH-RH receptor antagonists and (B) branched cyclodextrincarboxylic acid [e.g. 6-O-cyclomaltoheptaoxyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid Na salt] to improve their solubility, bioavailability and stability. Solubility of 3-(N-benzyl-N-methylaminomethyl)-4,7-dihydro-7-(2,6-difluorobenzyl)-5-benzoyl-2-(4-isobutylaminophenyl)-4-oxoethieno[2,3-b]pyridine in the presence of 6-O-cyclomaltoheptaoxyl-(6→1)-α-D-glucosyl-(4→1)-O-α-D-glucuronic acid Na salt was 20.5 mg/mL vs. 0.5 mg/mL.

L2 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:511666 CAPLUS
DOCUMENT NUMBER: 129:255149
TITLE: Multiple dose protocol for the administration of GnRH-antagonists in IVF: the "Lubeck-protocol"
AUTHOR(S): Felberbaum, R.; Diedrich, K.
CORPORATE SOURCE: Department of Obsterics and Gynecology, Medical University of Lubeck (D), Germany
SOURCE: In Vitro Fertilization and Assisted Reproduction, Proceedings of the World Congress of in Vitro Fertilization and Assisted Reproduction, Vancouver, B. C., May 24-28, 1997 (1997), 397-404. Editor(s): Gomel, Victor; Leung, Peter C. K. Monduzzi Editore: Bologna, Italy.
CODEN: 66MRAP
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Due to their different pharmacol. mode of action GnRH-antagonists are able to suppress serum-concns. of LH within hours. Instead of "down-regulation" and "desensitization" a classic competitive blockage of the GnRH-receptors on the cell-membrane of the gonadotrophic cells seems to take place. The "flare up", typical for agonistic GnRH-analogs is completely avoided. While the first generation of GnRH-antagonists caused important problems due to allergic reactions, which inhibited their clin. introduction, Cetrorelix and Ganirelix as representatives of the youngest generation of these compds. seem to avoid these disturbances completely. Cetrorelix was introduced first in our IVF-program to scrutinize the possibility of avoiding premature LH-surges. All patients were treated with human menopausal gonadotropin (HMG), starting on day 2. From day 7 until induction of ovulation by human chorionic gonadotropin (HCG)

Cetrorelix is administered s.c. in a daily fashion. Starting with a dosage of 3-mg Cetrorelix/day no premature LH-surges could be observed Also, 1 mg/day, 0.5 mg/day and 0.
25 mg/day administered according to the described "Lubeck-protocol" avoided any premature LH-surges. The mean courses of FSH and LH in the different dosage groups were quite similar with a profound suppression of LH. Estradiol concns. reflected a satisfactory follicular development. The fertilization-rate after IVF in cases of tubal infertility or ICSI in cases of male subfertility were within the range to be expected after normal oocyte maturation.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:1819 CAPLUS
DOCUMENT NUMBER: 126:55018
TITLE: Hormonal profile during the follicular phase in cycles stimulated with a combination of human menopausal gonadotropin and gonadotropin-releasing hormone antagonist (Cetrorelix)
AUTHOR(S): Albano, C.; Smitz, J.; Camus, M.; Riethmuller-Winzen, H.; Siebert-Weigel, M.; Diedrich, K.; Van Steirteghem, A. C.; Devroey, P.
CORPORATE SOURCE: Centre for Reproductive Medicine, University Hospital and Medical School, Dutch-speaking Brussels Free University, Brussels, 1090, Belg.
SOURCE: Human Reproduction (1996), 11(10), 2114-2118
CODEN: HUREEE; ISSN: 0268-1161
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A third-generation gonadotropin-releasing hormone antagonist (Cetrorelix) was used during ovarian stimulation in 32 patients undergoing assisted reproduction, to prevent the premature LH surge. In all patients, ovarian stimulation was carried out with two or three ampoules of human menopausal gonadotropin (HMG), starting on day 2 of the menstrual cycle. In addition, 0.5 mg of Cetrorelix was administered daily
from day 6 of HMG treatment until the day of ovulation induction by human chorionic gonadotropin (HCG). A significant drop in plasma LH concentration was
observed within a few hours of the first administration of Cetrorelix. Moreover, no LH surge was detected at any point in the treatment period in any of the 32 patients. A mean estradiol concentration of 2122±935 ng/l was observed on the day of the HCG administration, indicating normal folliculogenesis. Like LH, progesterone concentration also dropped within a few
hours of the first administration of Cetrorelix. A 0.5
mg daily dose of Cetrorelix prevented a premature LH surge in all the 32 patients treated.

L2 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:249914 CAPLUS
DOCUMENT NUMBER: 124:279399
TITLE: A new method for controlling the precise time of occurrence of the preovulatory gonadotropin surge in superovulated goats
AUTHOR(S): Baril, G.; Pougnard, J. L.; Freitas, V. J. F.; Leboeuf, B.; Saumande, J.
CORPORATE SOURCE: Station de Physiologie de la Reproduction des Mammiferes Domestiques, Institut National de la Recherche Agronomique, Nouzilly, 37380, Fr.
SOURCE: Theriogenology (1996), 45(3), 697-706

CODEN: THGNBO; ISSN: 0093-691X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In goats treated to induce superovulation, insemination at a predetd. time after the end of progestagen treatment leads to a low fertilization rate. To solve this problem we developed a new treatment based on the control of the occurrence of the endogenous LH peak with a GnRH antagonist (Antarelix). The first experiment was designed to determine the dose of LH required to mimic a spontaneous LH preovulatory discharge; the injection of 3 mg, i.v. of pLH induced a peak of the same amplitude and duration as the spontaneous peak. Subsequently, in the second experiment, we compared 2 doses of Antarelix (0.5 and 1 mg, s.c.) administered 12 h after sponge removal (9 goats/treatment group). The dose of 0.5 mg was selected for further expts. because it was effective in the inhibition of the endogenous LH peak and had no detrimental effect on the quality of embryos. In the final experiment, 48 goats received the new treatment and were inseminated (intrauterine) only once 16 h after LH injection; 41 were flushed and produced 5.3 (m) transferable embryos. The developmental stage and the number of cells/embryo were within the range that has been reported for embryos produced with conventional treatments. In conclusion, with the described method, it is possible to inseminate goats at a predetd. time without decreasing the number of transferable embryos. This technique will encourage the development of embryo transfer within genetic programs, and it will be a valuable tool for the production of zygotes for gene transfer.

L2 ANSWER 21 OF 25 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 92175455 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1794654
TITLE: Acute and subchronic toxicity studies with detirelix, a luteinizing hormone-releasing hormone antagonist, in the rat and monkey.
AUTHOR: Chester A E; Fairchild D G; Depass L R
CORPORATE SOURCE: Institute of Toxicologic Sciences, Syntex Research/R2-ITS, Palo Alto, California 94303.
SOURCE: Fundamental and applied toxicology : official journal of the Society of Toxicology, (1991 Oct) Vol. 17, No. 3, pp. 505-18.
Journal code: 8200838. ISSN: 0272-0590.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199204
ENTRY DATE: Entered STN: 24 Apr 1992
Last Updated on STN: 24 Apr 1992
Entered Medline: 6 Apr 1992
AB Acute (single dose), 2-week, and 3-month toxicology studies were conducted with detirelix, a luteinizing hormone-releasing hormone (LHRH) antagonist, in rats and cynomolgus monkeys. Acute studies were conducted by intravenous and subcutaneous injection. Subchronic studies were conducted by daily subcutaneous injection. Clinical signs after a single intravenous dose included lethargy, edema, cyanosis, pallor, and red ears in rats at greater than or equal to 0.3 mg/kg and lethargy and facial flushing in monkeys at greater than or equal to 0. 5 mg/kg. In subchronic studies, detirelix at greater than or equal to 0.4 mg/kg/day (rats) and at greater than or equal to 0.2 mg/kg/day (monkeys) produced atrophy of the reproductive organs, inhibition of ovulation and spermatogenesis, decreased body weight gain in

male rats and monkeys, and increased body weight gain in female rats. In the rat, morbidity and/or mortality occurred throughout the treatment phase at a subcutaneous dose of greater than or equal to 2.0 mg/kg/day. In both species, the time to recovery of normal reproductive organ morphology and function was directly related to dose. Exogenous testosterone decreased the severity of reproductive and body weight effects in male rats. In conclusion, the acute effects of detirelix were consistent with peripheral vasodilation. Subchronic effects were associated with inhibition of pituitary gonadotropic and gonadal hormone secretion.

L2 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1991:841 CAPLUS
DOCUMENT NUMBER: 114:841
TITLE: Gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists do not alter endogenous GnRH secretion in short-term castrated rams
AUTHOR(S): Caraty, Alain; Locatelli, Alain; Delaleu, Bernadette; Spitz, Irving M.; Schatz, Bernard; Bouchard, Philippe
CORPORATE SOURCE: Stn. Physiol. Reprod., Inst. Natl. Rech. Agron., Nouzilly, 37380, Fr.
SOURCE: Endocrinology (1990), 127(5), 2523-9
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To determine if GnRH analogs act on GnRH secretion through a short or ultrashort loop feedback mechanism, expts. were performed to analyze GnRH secretion in hypophyseal portal blood of conscious short-term castrated rams under both agonist or antagonist treatment. In Study 1, rams were castrated and surgically prepared for portal blood collection on day -7. Portal and peripheral blood were collected simultaneously every 10 min for 14-15 h on day 0. Five h after the beginning of the portal blood collection, animals were injected i.m. with 5 mg potent GnRH antagonist (Nal-Glu). In Study 2, rams were treated daily from day -11 to day 0 with the GnRH agonist D-Trp6 GnRH (0.5 mg i.m.).
Castration and surgical preparation for portal blood collection were performed on day -7. On day 0 portal and peripheral blood were collected simultaneously every 10 min for 10-11 h. In both studies, to determine whether an increase in GnRH concentration in hypophyseal portal blood can overcome the inhibitory effect of the GnRH analogs, between 5 and 5.5 h after the injection of the analogs, endogenous GnRH secretion was stimulated by naloxone administration (3 + 100 mg, i.v., at 30-min intervals) followed by a bolus of exogenous GnRH (2 + 10 μg, i.v., at 30-min intervals). In study 1, Nal-Glu administration led to a rapid cessation of pulsatile LH secretion for the duration of blood collection, whereas GnRH pulse frequency and amplitude were not affected. GnRH and LH pulse frequency before and after Nal-Glu administration were, 6.2 vs. 5.7 and 5.3 vs. 0.3 pulses/6 h, resp. In Study 2, peripheral LH secretion was completely suppressed, whereas GnRH secretion (portal blood) remained pulsatile. GnRH pulses frequency and pulse amplitude were 4.3 pulses/6 h and 43.0 7 pg/mL, resp. In both expts., neither stimulation of endogenous GnRH secretion by naloxone nor administration of exogenous GnRH allowed reinitiation of LH secretion. However, addnl. studies in animals of each treatment group (study III) showed that this was clearly a dose-related effect in antagonist treated but not in agonist-treated animals since higher doses of exogenous GnRH (i.e. 100 μg or 1000 μg) can increase LH levels. Thus, in short-term castrated ram, neither GnRH agonist nor GnRH antagonist administration affect endogenous GnRH secretion either directly by an action on GnRH neurons or indirectly by a decrease in LH secretion. These results, therefore, do not support a role for both a short loop and ultrashort loop feedback mechanism in castrated rams.

L2 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1988:400976 CAPLUS
DOCUMENT NUMBER: 109:976
TITLE: Hormonal effects of single gonadotropin-releasing hormone antagonist doses in men
AUTHOR(S): Jockenhovel, F.; Bhasin, S.; Steiner, B. S.; Rivier, J. E.; Vale, W. W.; Swerdloff, R. S.
CORPORATE SOURCE: Harbor-UCLA Med. Cent., Torrance, CA, 90509, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (1988), 66(5), 1065-70
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To assess its gonadotropin-inhibiting potency in man, different doses of a gonadotropin-releasing hormone (GnRH) antagonist ([Ac-D2-Nal1,D4-Cl-Phe2, D3-Pal3, Arg5,D4-p-methoxybenzoyl-2-amino butyric acid6,D-Ala10]GnRH) (I) were given to normal men. Single s.c. doses of 0.5, 1.5, and 5.0 mg I decreased mean serum immunoactive LH (iLH), to 45.0, 37.0, and 31.3% of baseline, resp. Maximal suppression occurred between 4 and 8 h after drug injection. Serum bioassayable LH concns. diminished 8 h after injection of 1.5 and 5.0 mg I, but not after the 0.5-mg dose. Mean serum testosterone (T) fell to 39.8, 32.1, and 20.7% of baseline, resp., after the 0.5-, 1.5-, and 5.0-mg doses. The decreases in serum iLH and testosterone (T) were more sustained after the higher doses; serum iLH and T were suppressed 24 h after administration of the 5.0-mg dose. The 24-h integrated serum iLH and T concns. decreased in a dose-dependent manner. However, basal and 24-h integrated serum FSH concns. were not affected by I. No adverse systemic side-effects occurred. Thus, I effectively decreases serum LH and T concns. in a dose- and time-dependent manner, and it, therefore, has potential as a male contraceptive.

L2 ANSWER 24 OF 25 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 83261620 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6409590
TITLE: Is the postovulatory release of follicle-stimulating hormone in the rabbit mediated by luteinizing hormone-releasing hormone?.
AUTHOR: Mills T M; Copland J A; Coy D H; Schally A V
CONTRACT NUMBER: BRSG-S-07RR05365-21 (United States NCRR)
HD-0-2831 (United States NICHD)
HD-16431 (United States NICHD)
SOURCE: Endocrinology, (1983 Sep) Vol. 113, No. 3, pp. 1020-4.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198309
ENTRY DATE: Entered STN: 19 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 23 Sep 1983
AB Studies were performed to determine whether the postovulatory secretion of FSH in the rabbit is an LHRH-mediated event. Does were mated and then injected at 12 and 18 h postcoitum with pentobarbital (30 mg/kg BW), an agent known to block endogenous LHRH release. The injection of this barbiturate had no measurable effect on the postovulatory FSH secretion pattern. Administration of the LHRH antagonist [Ac-D-p-Cl-Phe1,2, Phe3, D-Arg6, D-Ala10]LHRH (0.5 mg/doe) prevented all gonadotropin release in response to LHRH injection (10 micrograms/kg BW). When this same dose of the antagonist

was injected at 18 h postcoitum, the postovulatory FSH secretion pattern was unaffected. Finally, to prove that the pituitary was sensitive to LHRH at 18-h postcoitum, LHRH (10 micrograms/kg BW) was injected into rabbits mated 18 h earlier; this treatment led to a marked increase in FSH secretion showing that the pituitary is responsive to LHRH at this time. The results of this study show that two drugs which block LHRH-mediated gonadotropin release have no effect on the postovulatory secretion of FSH and support the concept that this episode of FSH secretion occurs via a pathway which does not include the hypothalamic secretion of LHRH.

L2 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1982:593440 CAPLUS
DOCUMENT NUMBER: 97:193440
ORIGINAL REFERENCE NO.: 97:32237a,32240a
TITLE: Suppression of ovulation in the rat by an orally active antagonist of luteinizing hormone-releasing hormone
AUTHOR(S): Nekola, M. V.; Horvath, A.; Ge, L. J.; Coy, D. H.; Schally, A. V.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Science (Washington, DC, United States) (1982), 218(4568), 160-2
CODEN: SCIEAS; ISSN: 0036-8075
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A synthetic antagonist of LH-RH [N-acetyl-D-p-chloro-Phe1,2-D-Trp3-D-Arg6-D-Ala10]-LH-RH (I) [83539-08-6] blocked ovulation in rats in a dose-dependent manner when given by gavage on the afternoon of proestrus. Ovulation was delayed for at least 1 day in all animals given 2 mg I and in some of the animals treated with 1 or 0.5 mg. Oral administration of 2 mg also blocked the preovulatory surge of LH [9002-67-9]. This demonstration that antagonists of LH-RH can have oral antiovulatory activity clearly enhances their therapeutic potential.

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